Review

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Nanostructured boron agents for boron neutron capture therapy: a review of recent patents

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Abstract: Boron neutron capture therapy (BNCT) is a potential radiation therapy modality for cancer, and tumor-targeted stable boron-10 (^{10}B) delivery agents are an important component of BNCT. Currently, two low-molecular-weight boron-containing compounds, sodium mercaptoundecahydro-*closo*-dodecaborate (BSH) and boronophenylalanine (BPA), are mainly used in BNCT. Although both have suboptimal tumor selectivity, they have shown some therapeutic benefit in patients with high-grade glioma and several other tumors. To improve the efficacy of BNCT, great efforts have been devoted for the development of new boron delivery agents with better uptake and favorable pharmacokinetic profiles. This article reviews the application and research progress of boron nanomaterials as boron carriers in boron neutron capture therapy and hopes to stimulate people's interest in nanomaterial-based delivery agents by summarizing various kinds of boron nanomaterial patents disclosed in the past decade.

Keywords: boron agent; boron neutron capture therapy; dendrimer; drug delivery; nanomaterial

Introduction

The actual advancement of boron medicinal chemistry was considered to be initiated from the usage of boron neutron capture therapy (BNCT) in the treatment of cancer patients [1, 2]. The clinical treatment of cancers with the help of BNCT is associated with the accessibility of suitable neutrons sources and the expansion of nuclear research technology. The schematic diagram of BNCT is shown in Figure 1A. The BNCT is carried out by bombarding the stable boron-10 (^{10}B) isotope with either epithermal neutrons (10,000 eV) or low-energy (0.025 eV) thermal neutrons for clinical applications. During this process, high-linear energy transfer (LET) alpha (α) particles (^{4}He) and recoiling lithium-7 (^{7}Li) nuclei are produced as shown in Figure 1B. For a successful therapy, at least about 20 μg/g of ^{10}B per weight of tumor is essential to be accumulated in the tumor cells (about 10^{9} atoms/cell) [1]. Due to quite small pathlengths (5–9 μm) of α particles, their disparaging effects are restricted to cells containing boron. In principle, α particles can spare normal cells and selectively destroy tumor cells. Interest of BNCT in clinical applications is focused primarily on head and neck region recurrent tumors patients and high-grade gliomas [2–13]. Moreover, BNCT is applied on a smaller number of patients with lung cancer, cutaneous [14–17] or extra-cutaneous [18] melanomas.

The study of electron-deficient boron cluster materials has developed a major area of inorganic/organic, and metallic chemistry, which now considerably overlay with medicinal and organic chemistry. The mission of BNCT was facilitated in 1960s by the discovery of new polyhedral boron compounds which contain cluster of boron as an alternative to single boron atom per molecule [4–7]. Polyhedral boranes of bioorganic chemistry are new tendency in this field, which emerged new entities for tumors as boron carriers. Low molecular weight carborane-containing carbohydrates, nucleosides, amino acids, nucleic acids and bases, porphyrins, DNA groove binders, and lipids are among the new compounds used in BNCT [4–7]. In recent years, a new type of radiosensitizers including biopolymers covering one or more carboranyl deposit was defined for BNCT. Boron agents of this class includes carboranyl peptides, carboranyl oligophosphates, nucleic acids (DNA-oligonucleotides), and proteins [6, 8, 9]. Nevertheless, there are ups and downs in the interest of using BNCT and it is still not applied for useful clinical applications. However, rudimentary information of boron compounds about pharmacokinetics and toxicity has been obtained by extensive study on boron carriers for BNCT, which can be beneficial for the expansion of boron compounds for other applications. During these years, molecules of boron cage and their complexes have been studied for various biological activities, including anti-rheumatoid

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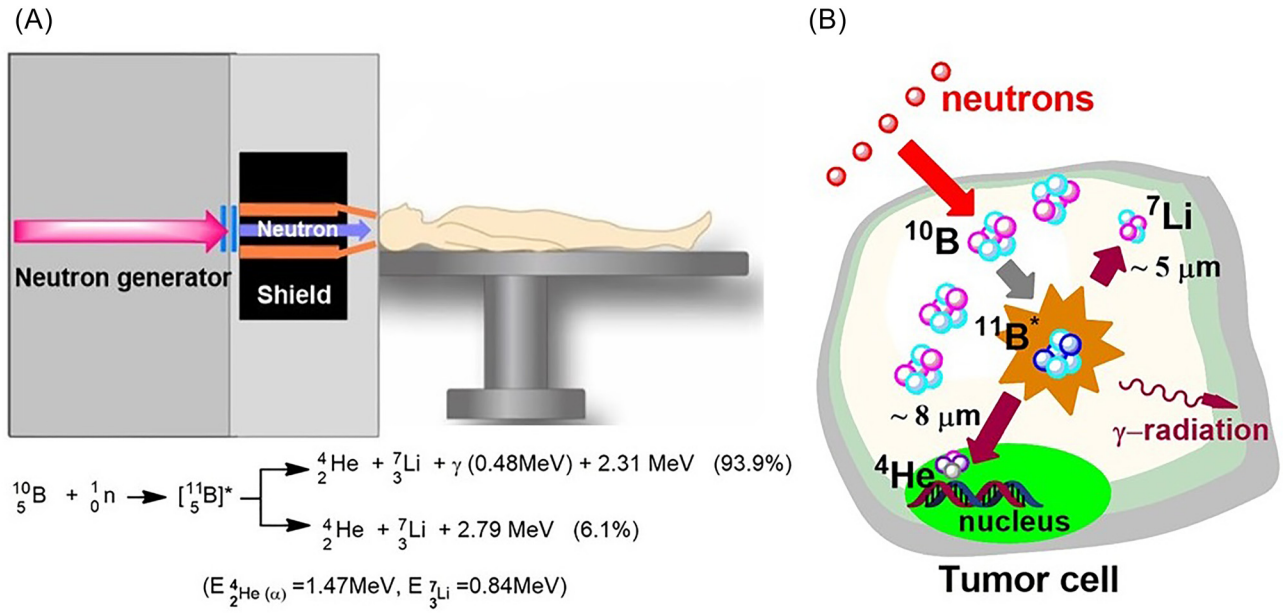

Figure 1: Principle for boron neutron capture therapy (BNCT). (A) Schematic illustration of BNCT system. (B) Schematic diagram of the cell-killing mechanism of BNCT.

arthritis activity, anti-human immunodeficiency virus (HIV) activity, drug delivery, anticancer activity, and imaging for diagnosis and treatment [10–13].

These newly outcomes obviously exhibit that still unexplored boron-containing compounds have great potential in bioorganic chemistry and medical applications. It is not mandatory that for drug discovery, boron is the only solution; however, boron is a good addition in the medicinal chemistry toolbox. About thirty years before fluorine has the same status in medicinal chemistry as boron; however, fluorine compounds are now produced on a repetitive basis in pharmaceutical study and hold a significant share in the medicinal marketplace. The drug correspondents with diversity of biological events of boron solo atom or cluster fragments demonstrate that additional exploration is still waiting to emerge in boronated medicinal chemistry. Recently, numerous books and review articles have been published relating to boron and its applications displaying its developments in medicinal chemistry [9, 13–26], but here we are hoping to reveal about the immense applications of boron chemistry by focusing on the neutron capture therapy drug for the treatment of cancer.

BNCT for cancer treatments

Tumor in brain

The BNCT application for tumors in the brain was applied in clinics for the first time in 1950s in the United States at Brookhaven National Laboratory [27, 28]. However, the median survival of patients was only 87 days subsequently applying BNCT. In 1990s, the epithermal beams were used for BNCT in Japan, Germany, United States, Czech Republic, Sweden, Finland and Taiwan, China. Therefore, BNCT therapeutic possibilities and biological impacts have been very much enhanced afterwards. The development of ^{18}F-BPA-PET in Japan was the main reason for this development. Previously, it was reported that 167 cases of high-grade meningiomas and malignant brain tumors were treated with BNCT. Using boronophenylalanine (BPA) in BNCT for recurrent glioblastoma, the median survival time was 10.8 months. While the combination of BPA and sodium borocaptate (BSH) in BNCT for newly diagnosed glioblastoma has showed the survival period of 23.5 months with a boost in X-ray and 15.6 months without using any X-ray boost [29].

In recent years, the BNCT treatments were executed on 34 affected people having deadly, final-stage tumors in brain, as reported by Chen et al. [30]. It was observed that it has no severe adverse events (AEs) (grade ≥3). The disease control rate and objective response were 85.3 % and 50.0 %, respectively. The recurrence-free survival (RFS), cancer-specific survival (CSS), and mean overall survival (OS) times were 4.18, 7.80, and 7.25 months, respectively [30].

Recently, in March 2020, Japan Ministry of Health, Labor and Welfare department approved a cyclotron-based accelerator neutron source which was recently constructed by Sumitomo Heavy Industries [31]. This accelerator-based BNCT safety and efficacy was assessed in 27 recurrent

glioblastoma patients using ^{10}B-boronophenylalanine by Kawabata et al. [32]. It was found that the 1-year survival rate was 79.2 % and median OS was 18.9 months [30].

Recently, a delivery system based on boron that includes the cerebrospinal fluid (CSF) was developed to improve the therapeutic efficacy of BNCT. This method involves intravenous administration which is totally opposite of the conventional method [33]. Boron uptake from the BPA delivery agent by the brain cells, as well as the profile of boron time-concentration, were also examined in lateral ventricle of normal rats in the CSF. A comparable brain cell uptake levels were achieved by using CSF-based and IV administration methods. However, lower BPA doses were involved in the former method than the latter one. These findings suggest that the economic and physical burdens may be reduced using the CSF method for brain tumor patients.

Cancer in head and neck

Patients with locally advanced cancer in head and neck regions, which is inoperable were treated with BNCT in clinical phase I/II trials which were held in Finland from 2003 and September 2008 as reported by Kankaanranta et al. [34]. In these patients, 76 % response rate was observed while only 30 % median progression-free survival (PFS) was detected in 7.5 months, and 20 % OS in 2-years. In another study, 79 patients with head and neck inoperable Squamous Cell Carcinoma (SSC) were treated in Espoo, Finland with L-BPA-mediated BNCT from February 2003 and January 2012 as reported by Koivunoro et al. [35]. As a result, 36 % complete response rate were observed while 68 % of these patients exhibited some recovery. The OS rate was 21 % and the 2-year locoregional PFS rate was 38 % [35].

Hepatocellular carcinoma

In Japan, multiple hepatocellular carcinoma patient was treated for the first time as reported by Suzuki et al. [36]. Because of compromised liver function, the left liver lobe with multiple tumors was treated with hepatic arterial chemoembolization and the right liver lobe was treated with BNCT. The tumors were remained stable in size for 1 month, which were treated with BNCT. But, unfortunately, due to liver dysfunction triggered by the development of hepatocellular carcinoma, the patient died 10 months after BNCT [36].

The multiple hepatocellular carcinomas in the liver left lobe treated with BNCT with selective intra-arterial infusion of BSH containing in water-in-oil-in-water emulsion was reported by Yangie et al. [37]. The size of the region of the tumor was remained steady for 3 months; however, the patient died after 7 months of BNCT due to tumor progression [37].

Malignant mesothelioma and lung cancer

Lung cancer can also be treated with BNCT as reported in numerous articles [38–40]. Its therapeutic effect was shown in animal models on lung metastases from colon carcinoma and clear cell sarcoma, demonstrating no toxicity on normal tissue [40, 41]. The F-BPA feasibility in BNCT for malignant pleural mesothelioma, which is inoperable was reported by Suzuki et al. [42–44]. The BNCT was applied on two patients with a malignant short spindle cell tumor and another with malignant pleural mesothelioma [42]. The tumor size remained unchanged for 3–6 months with no late toxicities. One study showed that the reduction in lung metastases can be enhanced by using the BPA-BNCT with nicotinamide (a hypoxia-releasing agent) or bevacizumab [45]. Another study shows that the number of lung metastases can be reduced by using BPA-BNCT with nicotinamide as well as in combination with both tirapazamine and mild temperature, while control of local tumor can be improved by using BSH-BNCT in the presence of tirapazamine, hypoxic cytotoxin, with or without mild temperature hyperthermia [46]. Besides, BNCT is also applicable for treating shallow lung tumor as reported by Farias et al. [47].

Skin melanoma

To investigate tumor control and skin toxicities in BNCT-based melanoma treatments, the dynamic infrared imaging was reported to be a useful and sensitive tool [48] in contrast with conventional radiotherapy, which is considered to have extremely non-uniform dose distributions in the skin. In Argentina, multiple subcutaneous skin metastases of melanoma patients (6 female and 1 male) with an average age of 64 (51–74) years were treated between October 2003 and June 2007 [49]. An infusion of BPA about 14 g/m^2 was applied for all patients, followed by a mixed thermal-epithermal neutron beam, showing no changes in 30.7 and 69.3 % of overall response considering evaluable nodules. Evaluable areas of 3 out of 10 showed ulceration suggesting that the toxicity was acceptable [49]. Recently, ^{10}B-enriched BPA-fructose complex infusion was studied for BNCT on three patients with skin melanomas [50]. The

skin/blood (S/B) and tumor/blood (T/B) ratios were calculated to find ^{10}B concentration in skin, blood and tumor. The S/B ratio for three patients with melanoma was in the range 0.81–1.99 and T/B was in the range 1.48–3.82 [50]. The ^{10}B concentration in skin was greater than that in blood, which was useful to evade over-dose in normal skin. Moreover, preclinical trial of MRI guided BNCT was performed on skin melanomas, head and neck recurrent and primary cancers and highly malignant brain tumors [51]. The main focus of the study was the efficient evaluation of theranostic agent for MRI guided BNCT. More recently, valproic acid (VPA) (a promising sensitizer for cancer therapies) was used concurrently with BNCT to enhance the effect of destroying melanoma cells [52]. The results showed that combining the action of VPA and BNCT could considerably constrain the growth of melanoma cells.

Boron agents for BNCT

Importance of the boron drug in BNCT

One of the major limitations of BNCT was the unavailability of tumor precise BNCT drugs with adequate tumor uptake. The ideal boron-based compound must satisfy a few conditions to be used in BNCT, such as high tumor/tissue and tumor/blood concentration ratios (>2.5:1), low toxicity in the living system, and speedy removal from healthy tissue and blood. However, its presence is necessary in the tumor for some time during irradiation with neutrons [53].

To improve low systemic toxicity with targeting tumor cells, three generations of boron compounds have been studied during the past several decades. Boric acid and its derivatives are considered as first generation of agents which was used in clinical trials from 1950s–1960s. These compounds exhibited deprived tumor retention time, low selectivity and imperfect tumor/brain ratios. The BPA and BSH are considered as compounds of second-generation which remained longer in tumors, displayed considerably lower toxicity, and attained the required tumor/brain and tumor/blood ratios. Currently, these drugs are used in clinical trials. The sorbitol-BPA injectable solution, approved in Japan in May 2020 (Steboronine), is based on advances in drug formulations and is one of the current generation of compounds. Development of boron clusters which are linked over a hydrolytically steady linkage with a tumor-targeting constituent or moiety is considered as the third-generation compounds. Agents of third generation include one or more polyhedral anions of carboranes or boranes, which will be discussed further in this review [54, 55].

Debut of the newly developed boron agent for BNCT

To date, two boron compounds, boronophenylalanine (BPA) and mercaptoundecahydrododecaborate-^{10}B (BSH), have been successfully applied in BNCT clinical trials [56]. The molecular structures of BPA and BSH are shown in Figure 2. The BPA is an amino acid derivative actively incorporated by tumor cells by the L-type amino acid transporter 1 (LAT1). BSH is a water-soluble diffusion drug, primarily used for malignant glioma. It accumulates in malignant brain tumors and thus does not cross the blood brain barrier (BBB) into the normal brain [57]. However, the accumulation of BSH in tumor cells is low and has poor membrane permeability [57, 58]. It is recognized that the two drugs show inherent disadvantages such as relatively low bio-selectivity of tumor to blood and sparing water solubility of pristine BPA. Although conjugating with fructose may improve water solubility of BPA, but a significant amount of BPA-fructose complex, used in clinic, is harmful to patient.

Nonetheless, BPA has been prepared on industrial scale in the Good Manufacturing Practices (GMP) facility for clinical application. For example, in Sunshine Lake Pharma Co, Ltd. in Guangdong, China, GMP standard process has been built up to produce high quality BPA, and so far, around 70 kg of BPA is obtained as investigational new drug (IND) in China. A few new neutron stations have also been built in China, such as BNCT centers in Dongguan general hospital and Xiamen Hongai hospital. New generation of the BNCT drugs are highly expected to overcome the draw backs of the BPA and BSH and comply with fast development of BNCT in Asian countries.

Both BPA and BSH compounds show several limitations despite their clinical usage. Great efforts have been devoted to construct more efficient boron agents. Over the past decade, the development of boron agents has taken into new directions, including small boron molecules and boron

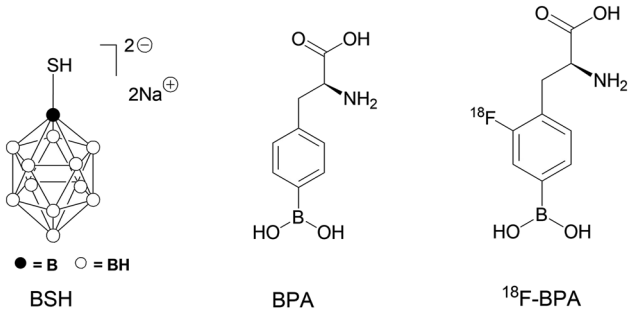

Figure 2: Structures of mercaptoundecahydrododecaborate (BSH), boronophenylalanine (BPA) and 2-^{18}F-boronophenylalanine (^{18}F-BPA).

delivery nanomaterials [59–66]. The new boron agents of small molecules have been well reviewed [15, 67, 68].

On the other hand, nanomaterial and nanoparticle distribution systems have attracted a lot of attention in recent decades and are an important area of interest in current research. The size of the nanoparticles can be defined as the material with structures on the nanoscale dimension (between 1 and 100 nm), and materials in this size range have many novel characteristics that are different from conventional solids, such as large specific surface area, high surface activity and quantum size effect. Nanomaterials have good application prospect in many aspects, including catalysis, biochemical sensing, biological detection, bio-imaging, drug carrier, semiconductor materials, etc. Because of their unique characteristics and properties, nanomaterial and nanoparticle distribution systems have the potential to offer advantages over conventional forms of drug molecules, with unique responses and localization of the effect in a range of therapeutic applications [69, 70]. In recent decades, the nanoparticle distribution systems have also been investigated as potential boron vectors for therapeutic boron neutron capture applications. In the following context, preclinical agents of boron delivery nanomaterials reported in the disclosed patents, such as dendrimers, liposomes and nanoparticles, are surveyed.

Boron-containing nanomaterials and nanoparticles for BNCT

Boron nanomaterials are materials with good optical, electrical and mechanical properties and are widely used as biomedicine, electronics and catalysts. The unique properties of boron nanomaterials are expected to improve the enrichment and selectivity of boron in cancer cells, making them excellent candidates for drug delivery and imaging applications. Boron nanomaterials have the characteristics of high specific surface area, high drug load, tunable morphology and size, good biocompatibility and biodegradability, etc., and can enhance their targeting and stability by surface modification or wrapping other functional molecules. Compared with classical small boron molecules, boron nanoparticles can deliver high concentrations of boron atoms into tumors due to their enhanced permeability and retention (EPR) effect or active targeting ability, while only a small amount of boron will be absorbed by surrounding normal tissues.

At present, several different types of boron nanomaterials have been synthesized and investigated as boron agents for BNCT. These materials can enter the body by intravenous, oral, or topical administration, and then be absorbed or attached to cancer cells, thereby improving the therapeutic effect of BNCT. Here, we focus on the progress of patent applications for nanomaterial-based boron delivery agents.

Dendrimers

Due to their low toxicity, diversity of reactive terminal groups, and potential incorporation of active target moieties, dendrimers have become an ideal platform for drug delivery and imaging applications. The epidermal growth factor (EGF), folic acid (FA), and vascular endothelial growth factor (VEGF) have been used to target dendrimers [71]. The patent CN104399094B [72] discloses a targeted boron agent, which is composed of polyamidoamine dendrimers, the EGFR (epidermal growth factor receptor) antibody and polyhedral boranes. The polyamide amine dendrimers are connected to the EGFR antibody, and are internally loaded with the polyhedral boranes. Accordingly, the polyamide monoamine dendrimer and EGFR antibody are connected by 3-(2-pyridinedimercapto) propanoic acid N-hydroxy-succinimide ester and undecanoic acid maleimide-hydrazides-trifluoroacetate to form functionalized dendritic macromolecules, and then loaded with polyhedral boranes to obtain the targeting boron agent.

The advantage includes: (1) the boron agent loads a large dose of polyhedral borane (BSH) in the cavity of the dendritic macromolecule, which significantly improved the dosage of boron atom, and it has the advantages of high envelop rate and high drug loading capacity, which also meets the requirements of BNCT on the boron atom dosage; (2) the boron agent is connected with the antibody highly expression on the tumor cells surface by EGFR (mAbEGFR), which has preferable targeting to tumor cell, increases the difference in the absorption of boron between tumor and normal cerebral tissue, reduces the damage to normal cerebral tissue caused by various meaningful rays during neutron irradiation, and has good stability and low cytotoxicity; (3) it can be effectively taken up by human glioma U87MG cells with high surface expression of EGFR; and (4) it can effectively improve the content of boron in the tumor tissue of orthotopic transplantation tumor nude mouse, and obviously prolong the life cycle of orthotopic transplantation tumor nude mice after neutron irradiation.

The same targeting strategy of the EGFR was also identified in WO2015189477A1 [73]. The patent discloses a conjugate with a pharmaceutical composition and a method of treating or modulating the growth of EGFR1 expressing

tumor cells in humans. The conjugate comprises an anti-EGFR1 antibody or an EGFR binding fragment and at least one dextran derivative, wherein the dextran derivative comprises at least one D-glucopyranosyl unit, in which at least one carbon is selected from carbon 2, 3 or 4 of one D-glucopyranosyl unit that is substituted by a substituent of the formula -O-(CH_2)n-S-$B_{12}H_{11}^{2-}$, where n is in the range of 3–10. The dextran derivative is bound to the anti-EGFR antibody or an EGFR1 binding fragment *via* a bond formed by a reaction between one aldehyde group by oxidative cleavage of a D-glucopyranosyl unit of the dextran derivative and an amino group of the anti-EGFR1 antibody or an EGFR1 binding fragment. The purpose of the invention is to provide conjugates that have improved properties as compared to known conjugates and that contain a high content of boron-10.

The "Dextran" refers to a branched glucan composed of chains of varying lengths, wherein the straight chain consists of α-1,6 glycosidic linkages between D-glucopyranosyl units. The "D-glucopyranosyl unit" refers to a single D-glucopyranosyl molecule. The branches are bound *via* α-1,3 glycosidic linkages and, to a lesser extent, *via* α-1,2 and/or α-1,4 glycosidic linkages. A portion of a straight chain of a dextran molecule is depicted in the schematic representation below in Figure 3.

Dendritic polyamides have also been studied as possible carriers of boron. Recently, Wei et al. reported the development of a molecule containing boron with the cell nucleus targeting property (CN110279858B) [74]. The nanomaterial is consisting of 1-bromomethyl o-carborane, 2nd-generation dendritic polyamide and hyaluronic acid or consisting of 4-boron-L-phenylalanine, di-tert-butyl dicarbonate and 2nd-generation dendritic polyamide comprising o-carborane and dendritic polyethyleneimine. The preparation of boron-containing species with the cell nucleus targeting property can further target and locate the tumor cell nucleus while showing better tumor cell uptake, and is a novel boron trapping agent with the cell nucleus targeting property. The preparation method comprises the following steps: (1) dissolving the cell nucleus targeting drug doxorubicin, containing active amino group, into dimethyl sulfoxide, adding triethylamine, stirring for 2–4 h, then adding 1-bromomethyl o-carborane, followed by stirring continuously for 48–60 h, and further adding diethyl ether to generate a precipitate. The molar ratio of the cell nucleus targeting drug to the triethylamine to the 1-bromomethyl o-carborane is 1:1:3; (2) collecting the precipitate, putting the precipitate into a dialysis bag, dialyzing for 24–30 h using dimethyl sulfoxide as a dialysate, or dialyzing for 48–60 h using distilled water as a dialysate, and performing freeze drying under reduced pressure to obtain the boron-containing species with the cell nucleus targeting property, however, the cut-off molecular weight of the dialysis bag is 300–500 [74].

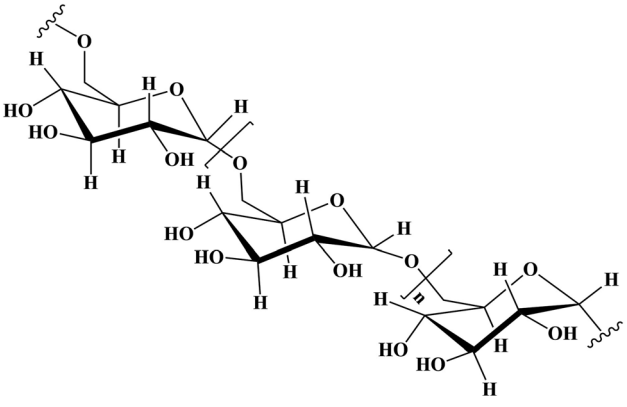

Figure 3: A portion of a straight chain of a dextran molecule.

Antibody-drug conjugates

The antibody-drug conjugates (ADCs) are an emerging class of targeted therapeutics with improved therapeutic indices when compared to traditional chemotherapy. In addition to monoclonal antibodies (mAbs) and target selection, drugs and linkers have been the focus of ADC development. It has been reported that the pharmacological profile of ADCs can be improved by applying site-specific conjugation techniques that utilize surface-exposed cysteine residues engineered into antibodies that are then conjugated to a linker drug, thereby producing site-specific conjugated ADCs with defined drug-to-antibody ratios (DARs). Site-specific conjugated ADCs typically exhibit at least equivalent *in vivo* efficacy, improved PK and an expanded therapeutic window relative to heterogeneous mixtures produced using conventional lysine and cysteine conjugation methods.

The ADC concept was adopted in the BNCT study to develop potentially efficient boron agents. The patent WO2021066869A1 [75] discloses antibodies that bind Her2, EGFR, Trop2, CDH3 or other TAAs containing a triple mutation at L234A, L235A, and L328C and methods of making such triple mutated antibodies are disclosed herein. Consequently, the triple mutated antibodies contain a modified effector function through Fc silencing and are capable of site-specific conjugation at L328C to form an antibody-drug-conjugate (ADC) which can be administered to patients and provide a method of treating cancer, immunological and neurological disorders.

The site-specific conjugation approach mediated by L328C was chosen to allow more homogeneous drug product and improved conjugation efficiency. Various therapeutic modalities including antibody drug conjugates (ADCs) can

benefit from site-specific conjugation as it can prevent formation of heterogeneous mixture, which can have negative effect on *in vivo* efficacy and therapeutic index. Similarly, attachment of boron-containing entities to specifically defined sites of antibody molecules could improve efficacy of Boron Neutron Capture Therapy (BNCT).

The conversion of Leu-328 to Cys in the Fc domain of monoclonal antibody allows controlled conjugation without affecting target binding. Moreover, neither the expression level nor the stability of antibody is compromised by introduction of L328C. Quality assessment *via* size-exclusion chromatography shows >99 % main peak, comparable to the wild-type counterpart. Thus, aggregation propensity often associated with introduction of unpaired cysteine is not observed for L328C. The uniform product formation with 100 % conjugation efficiency mediated by L328C implicates simpler manufacturing process as compared to complicated and inefficient production process required for non-specifically conjugated counterparts. Defined and homogeneous composition mediated through L328C conjugation, with much reduced therapeutic liabilities and simpler manufacturing process, enable accelerated discovery and development of ADCs and antibody boron conjugates for the application of BNCT.

The patent US11219689B2 [76] claims compositions comprising boron enriched linkers (BELs) that are synthesized for use as boron agents. In certain embodiments, the BELs comprise one or more boron clusters operably linked to a ligand, such as an antibody to create an antibody boron conjugate (ABC) (Figure 4). In a further embodiment, an ABC of the invention comprises a boron antibody ratio (BAR) from about 12 to several hundred or several thousand.

Liposomes

Liposomes are non-toxic, universal, small, and lipid-based natural nanomaterials and conventional drug delivery vectors that consist of cholesterol and natural non-toxic phospholipids. Targeting can be achieved by embedding suitable targeting proteins in the lipid bilayer of the liposome. Previous studies have shown that tumor cells have higher uptake of drugs encapsulated in liposomes when compared to surrounding normal cells. This can be partly attributed to the relative ease of modifying the surface of liposomes to achieve selective localization in tumor cells. Typically, liposomes are used as boron drug carriers in BNCT for the treatment of gliomas.

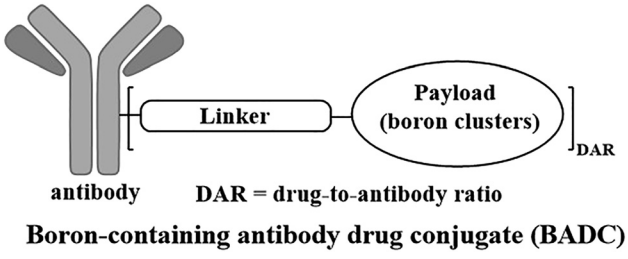

Figure 4: A general schematic representation of a boron-containing antibody drug conjugate.

In the patent CN104558585B [77], Fu et al. claim a lipid material that consists of two parts by taking polyethylene glycol as bridging in which one side of the part is connected with cholesterol, and the other side is connected with ascorbic acid or by taking polyethylene glycol as bridging with one side is connected with cholesterol, and the other side is connected with iRGD (CRGDKGPDC) tumor penetrating peptides. The structures of the two parts of lipid material are shown in Figure 5.

The lipid material has the potential to target the brain and deliver drugs deeply into tumor, which can effectively improve the curative effect of brain tumors. The lipid material can be used to develop different dosage forms, such as liposome, micelles, emulsions, and can be used for boron neutron capture therapy of brain glioma, which has broad application prospects.

Patent CN113750047A [78] refers to a multifunctional nano-liposome used in the BNCT. It provides a multifunctional nanoliposome, a preparation method and application thereof in boron neutron capture-immune-chemotherapy which is a combination therapy. The multifunctional nanoliposome includes adriamycin, carborane, cationic liposome, plasmids and peptides. On the basis of an unprecedented novel boron agent with nucleus tropism of cell, a multifunctional nanoliposome drug delivery system was constructed in combination with CD47 blocking immunotherapy. The resulting therapeutic effect of boron neutron capture-immuno-chemotherapy was explored in an *in-situ* glioma animal model. In the experiment, the realization of immunotherapy is mainly based on the targeted delivery capability of the iRGD mixed liposome, and the CRISPR/Cas9 gene knockout plasmid aiming at the CD47 gene is targeting to tumor tissue cells as much as possible. Since normal tissue cells lack the series of ‘eat me’ signals specific to tumor cells, it is relatively difficult to initiate a strong immune response even if the ‘don’t eat me’ signals are reduced in normal tissue cells.

Polymeric nanoparticles

Polymeric nanoparticles have become one of the most promising forms of drug delivery platforms in nanomedicine

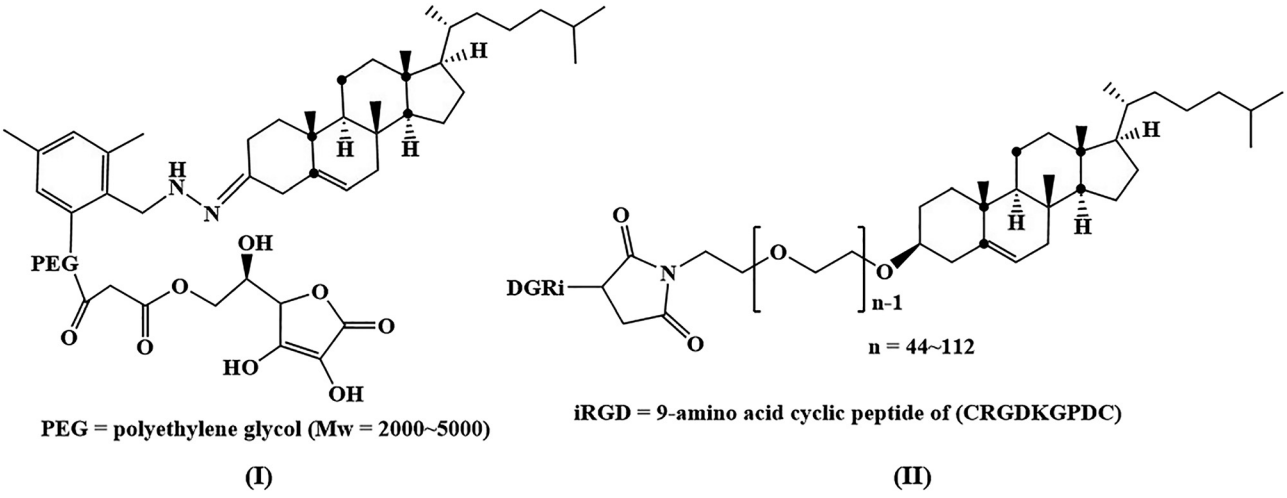

Figure 5: The structure of the two parts of the lipid material.

due to their controlled synthesis, excellent stability, high water solubilization, and increased accumulation in tumors. In addition to the advantages of conventional drug delivery systems, such as improving drug solubility, increasing drug stability and sustained release, natural polymeric nanoparticles can also change the tissue distribution and metabolism of drugs, improve drug efficacy and reduce systemic toxic side effect of drugs, and have great clinical application value.

The patent CN101879427B [79] claims a natural polymer-poly(3-acrylamido phenyl boronic acid) composite nanosphere. Its surface is hydrophilic natural polymer, and the interior is hydrophobic poly(3-acrylamido phenyl boronic acid). The number-average molecular weight of the natural polymer is in the range of 2000–100,000, the content is 5 %–70 % of the mass of the composite nanospheres, and the number-average molecular weight of poly(3-acrylamido phenyl boronic acid) is in the range of 1000–10,000, and the content is 30 %–95 % of the mass of the composite nanospheres. The average particle size of the nanospheres is 40–100 nm. The composite nanospheres have the characteristics of high biocompatibility and stable chemical properties. The composite nanospheres is a boron carrier which has a sustained release effect and can be used as a carrier agent in boron neutron capture therapy.

The patent WO2014133547A1 [80] discloses another type of borate polymer nanoparticles. It is composed by a polymer containing a polyol coupled to a polymer containing a boronic acid, configured to present the polymer containing a boronic acid to the nanoparticle, externally. As a related patent, WO2014133549A1 [81] discloses nanoparticles comprising a polymer containing a polyol and a polymer containing a nitrophenyl boronic acid, wherein the polymer containing a nitrophenyl boronic acid is coupled to the polymer containing a polyol with a reversible covalent linkage, which enhances the stability of the nanoparticle by reducing its pKa. The nanoparticle further comprises ^{10}B as part of at least one polymer containing a nitrophenyl boronic acid with the composition being formulated for *in vivo* boron neutron activation therapy.

The patent CN109125739B [82] discloses a multifunctional high-molecular polymer micelle drug delivery system with a method of preparation and application thereof that relates to the technical field of targeted drug delivery. A part of side chains of a polyethylene glycol-polylysine block copolymer is chemically modified by 3,3′-dithio-bisalanine dimethyl ester dihydrochloride to obtain groups with sulfhydryl, and then resulting drugs, namely sulfhydryl dodecaborane disodium salt for boron neutron capture treatment. The sulfhydryl groups are reacted with the side chains in an aqueous solution through disulfide bonds to form stable multifunctional high-molecular micelles through self-assembly and partial free disulfide bond crosslinking. The resulting high molecular micelle can deliver sulfhydryl-containing disodium dodecaborane or other sulfhydryl-containing drugs or prodrugs, as shown in Figure 6A, so that the content of the drugs delivered into tumor cells is increased, and the targeted treatment effect on tumors is improved. The multifunctional polymer micelle drug delivery system with disulfide bonds can respond to high-concentrations of glutathione in tumor cells for crosslinking micelle cores and crosslinking with drugs, which can achieve controlled drug release and micelle dissociation. The polycations in the macromolecular micelles have the function of destroying lysosomes and endosomes during

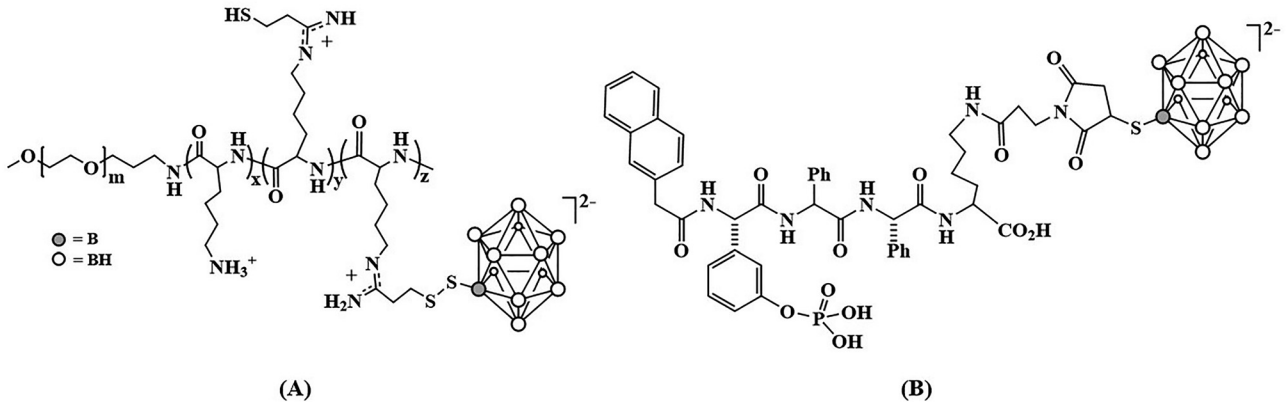

Figure 6: The structures of the mercaptododecaborane disodium salt cross-linked block copolymer (A) and the boron-doped tumor targeted drug (B).

the endocytosis of tumor cells, realizing the purpose of high-efficiency drug delivery to the tumor cells. Nonetheless, the existing drugs are difficult to target tumor cells and insufficient drug delivery to tumor cells and other issues are to be investigated.

Poly(ε-caprolactone)-poly(ethylene glycol)-succinic ester (PCL-PEG-NHS) is a biodegradable amphiphilic copolymer with amine-reactive ester group at the PEG end. PCL-PEG-NHS is used to prepare polymeric micelle where its PEG shell can be altered by targeting moieties, and hydrophobic drugs like paclitaxel can be packed in its PLA core. Gong et al. (CN111281975A) [83] disclose a preparation method of a boron-containing nano-targeting drug using the PCL-PEG-NHS. The method comprises the following steps: (1) dissolving an amphiphilic polymer in an organic solvent to obtain an organic solution; adding a boron-containing medicament into an aqueous solution containing an emulsifier, uniformly mixing, then dropwise adding the obtained mixture into the organic solution, and stirring to obtain a water in oil (w/o) emulsion; (2) dropwise adding the w/o emulsion into the other part of aqueous solution containing the emulsifier, stirring, and then removing the organic solvent to obtain w/o/w double emulsion; and (4) freeze-drying the w/o/w double emulsion to obtain the boron-containing nano targeted drug. The preparation process of the boron-containing nano targeted drug is simple and convenient, the synthetic condition is mild, and the method is favorable for expanded production. Compared with free BPA, the tumor-to-blood ratio of the nano-targeted drug prepared by this invention is remarkably improved to 4.1:1, which could remarkably improve the therapeutic effect of tumor, and the nano-targeted drug has a very good application prospect when used as an anti-tumor drug alone or being combined with anti-tumor drugs such as paclitaxel.

Polypeptides

Peptide medication delivery systems have demonstrated many advantages over synthetic systems. They have improved biocompatibility, biochemical and biophysical properties, reduced toxicity, molecular weight controlled by synthesis and purification in solid phase. Peptide-based drug delivery platforms are used as peptide-drug conjugates, injectable biodegradable particles and depots for delivering small molecule pharmaceutical substances and therapeutic proteins. The patent CN113318227B [84] disclosed a boron-doped tumor targeted drug that comprises polypeptide, hydrophobic molecules located at the nitrogen tail end of the polypeptide, and mercaptododecaborane disodium salt located on lysine of the polypeptide. The amino acids forming the polypeptide include phosphorylated L-tyrosine, L-lysine, and L-phenylalanine. The drug can achieve specific enrichment in tumor cells, and the enrichment amount of each tumor cell can reach 37.3×10^9 B atoms, which meets the requirement of boron neutron capture therapy. In addition, the boron-containing drug has good biocompatibility, low immunogenicity and low toxicity. The preparation of the boron drug adopts a classical solid-phase synthesis method, the operation is simple, and the obtained boron-doped tumor targeted drug has the advantages of high chemical purity and high total yield. The molecular structure of boron-doped tumor targeted drug is shown in Figure 6B.

In CN115417889A [85], Deng et al. reported a monomer L-4-dihydroxyboron-phenylalanine-N-carboxylic anhydride and polyamino acids and their preparation methods and applications. It constructs a polypeptide nanomaterial with biological responsiveness and good biocompatibility, specifically involving the synthesis of L-4-dihydroxyboron-phenylalanine-N-carboxylic anhydride, as well as a series of polymers prepared from its ring opening polymerization

and applications in drug delivery. The polymers disclosed by the present invention have excellent biocompatibility and can be used to prepare (tumor targeting) polymer micelles, which are suitable for the efficient loading and delivery of hydrophilic and hydrophobic drugs, including drugs containing cis 1,2 or 1,3-diol, polypeptide drugs, protein drugs, nucleic acid drugs, etc.

On the other hand, it is well recognized that the solid form of a drug product has a significant impact on its physical properties, particularly solubility, dissolution rate, morphology and tableting characteristics. To overcome the solubility problem of BPA, Li et al. reported a nanocrystalline *p*-boronophenylalanine, its method of preparation, and application as a drug in boron neutron capture therapy in patent CN114949215B [86]. The sodium hydroxide solution of *p*-boronophenylalanine is mixed with hydrochloric acid and the resulting solution is added to polyvinyl pyrrolidone to yield nanocrystalline *p*-boronophenylalanine. This nanocrystalline has good water solubility. After lyophilization, the nanocrystalline is redissolved in water. The hydrated particle size is 58.0 ± 6.7 nm. After one month, the particle size is 64.0 ± 6.2 nm, with a slight increase in particle size and good stability. After the preparation of boron neutron capture therapy drugs from nanocrystalline *p*-boronophenylalanine, the boron concentration in tumor cells is significantly increased, in comparison with *p*-boronophenylalanine alone, with a boron concentration of 80 μg/mL and incubation time of 6, 12, and 24 h, while the survival rate of tumor cells significantly decreased after thermal neutron irradiation (Figure 7). The graph of cell survival rate comparison was obtained after the thermal neutron irradiation. It can be seen from the graph that the tumor cell survival rate of the *p*-boronophenylalanine nanocrystal prepared in the embodiment is significantly reduced when compared to that of the *p*-boronophenylalanine [86].

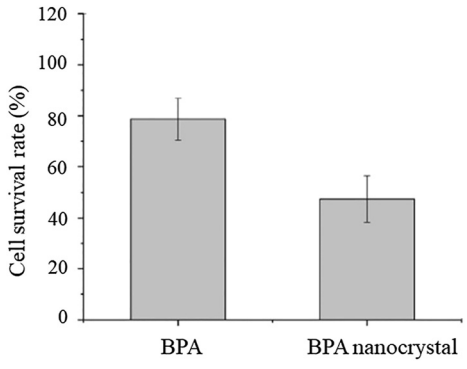

Figure 7: The graph of cell survival rate of the boronophenylalanine (BPA) and BPA nanocrystal.

Metal–organic frameworks

Metal-organic frameworks (MOFs), emerging in recent decades, have the characteristics of precision tunability, high drug loading capacity, good biocompatibility, and easy chemical modification, which meet the requirements of ideal drug carrier materials, and have attracted the attention of materials scientists and biomimetics researchers, particularly the researchers in biomedical field. MOFs have been used for delivery of boron agents in BNCT. The patent CN112587661B [87] reveals a zirconium-based porphyrin MOFs material containing boric acid, its method of preparation, and applications thereof. The zirconium-based MOFs material is loaded with boric acid into the pores of the porphyrin, with a particle diameter of 190 nm. The material has been characterized by Transmission Electron Microscope (TEM) (Figure 8A) and Scanning Electron Microscope (SEM) (Figure 8B). It was synthesized by the hydrothermal method, with mild reaction conditions, high synthesis efficiency, and good biocompatibility so that it can achieve the purpose of loading drugs in high-temperature environments. The drug loading capacity is high and has good active oxygen generation ability. The boric acid loading rate reaches 34 wt%. Experiments have shown that the boron loaded MOFs material can be targeted and enriched in brain glioma cells, indicating that it can be effectively ingested by cancer cells and can be used as a drug carrier for BNCT treatment.

In relative work, patent CN112587502B [88] discloses a membrane of red blood cells coated with nanoscale FOM as vectors of medicines, its method of preparation and its applications. The MOFs, as nano-scaled drug carrier, comprises nanoparticles of MOFs and red blood cell membranes. The pores of the MOFs nanoparticles are loaded with boric

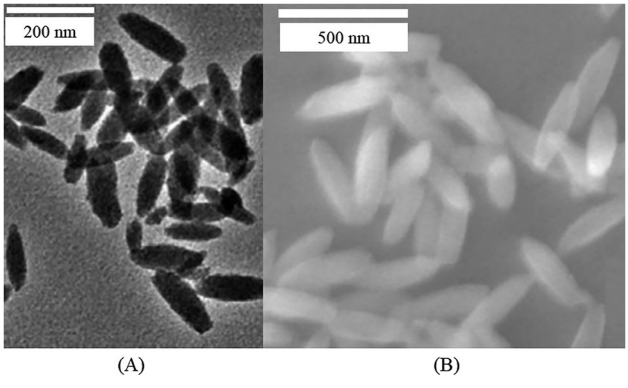

Figure 8: The transmission electron microscope (TEM) (A) and the scanning electron microscope (SEM) (B) diagrams of a boric acid-containing zirconium-based porphyrin metal-organic frameworks (MOFs) material embodiment.

acid, and the outer surface is coated with a red blood cell membrane. The MOFs nano-scaled drug carrier is synthesized by hydrothermal method under mild reaction conditions, with high synthetic efficiency, uniform particle size, good mono-dispersity, high drug loading, good fluorescence imaging ability, and high biocompatibility. It can be used as an anti-tumor drug carrier.

Covalent organic frameworks

Covalent organic frameworks (COFs) are a class of crystalline porous materials formed by covalent binding of organic molecular construction blocks. COFs have made many important advances in the fields of adsorption, catalysis and photovoltaics due to their new structures and excellent properties. Nevertheless, the pore size of COFs is difficult to control, and its hydrophilicity is low, which limits their applications. The patent CN114010783B [89] discloses a multifunctional boron rich nano-targeting agent based on a covalent organic framework material, its preparation method, and applications. This multifunctional boron rich nano-targeting agent based on a covalent organic framework material is prepared by self-assembly of a boron rich COF loaded with drugs and photosensitizers with the target. The boron rich COF is a periodic two-dimensional (2D) or three-dimensional (3D) network structure formed by dynamic covalent bonding of organic building blocks. It has characteristics such as large specific surface area, small density, high porosity, good stability, uniform pore size, structural adjustability, and functional diversity. The covalent organic framework modified by adding stabilizers containing abundant boron atoms can be used as excellent boron nanodrugs. In addition, due to its unique high specific surface area, $\pi - \pi$ stacking, and pore interaction, covalent organic frameworks have very high loading and encapsulation capabilities for hydrophobic and aromatic drugs and have unique advantages and potential application values in the efficient loading and delivery of immune adjuvants, photosensitizers, acoustic sensitizers, and chemotherapy drugs. The multifunctional boron rich nano targeted formulation crosses the barrier through surface modified DSPE-PEG2k-X molecules to achieve the joint delivery of ^{10}B, drug molecules, and photosensitizers within the tumor. Observing the distribution of drugs in cells through a fluorescence microscope and monitoring the distribution of nanoparticles *in vivo* in real-time can establish the optimal neutron irradiation conditions. Targeted radiation and immunotherapy of BNCT is achieved through simultaneous delivery of ^{10}B atoms and drug molecules within the tumor.

In patent CN114015066B [90], Liu et al. present a COF, which comprises a structural unit with a topological structure of a regular hexagon, the structural unit comprising a compound of formula I connected by an imine bond, and a compound comprising a core group and an arm group. The present invention adopts a multifunctional boron capsule with high biocompatibility. The essence of the boron capsule is a COF material containing carboranes, with a high specific surface area, high cavities, and nanoscale pores that can efficiently load hydrophobic drug molecules. The invention can combine BNCT with immunotherapy by using multifunctional boron capsules and achieve a systemic anti-tumor treatment effect by enhancing the BNCT effect of local tumors.

Magnetic nanoparticles

Magnetic resonance imaging (MRI)-detectable nanoparticles could be localized to the tumor sites by MR as imaging guided nanoparticles in BNCT. The patent CN110787295A [91] adopts the chemical vapor deposition (CVD) tube furnace high-temperature inorganic reaction method, and the boron source in the quartz tube is heated at high temperature in a reducing gas environment to exceed its melting point and then volatilize and is directly combined with the surface of the magnetic nanoparticle to obtain the nanoparticle with the core–shell structure. The invention is different from the preparation of BNCT boron agent by an organic solution method, and provides a simple, efficient, controllable and macro-preparation method of BNCT inorganic nanomaterial. The boron agent Fe_3O_4@B MNPs is a boron-coated superparamagnetic core–shell nanoparticle, and the nanoparticles are Fe_3O_4 NPs.

Boron-containing nanotubes and quantum dots

Carbon nanotubes and carbon quantum dots

Carbon nanotubes (CNTs) are allotropes of carbon in the form of cylindrical arrangements of carbon atoms. The CNTs are classified as single walled (SWCNT) or multi-walled (MWCNT). They have the unique property of being able to enter a variety of cells without showing significant toxic effects. The CNTs have become important nanomaterials for biomedical applications as carriers for drugs and other biomolecules. On the other hand, carbon quantum dots (CQDs) are a new kind of nanoscale functional carbon materials with a general size of less than 10 nm. With the

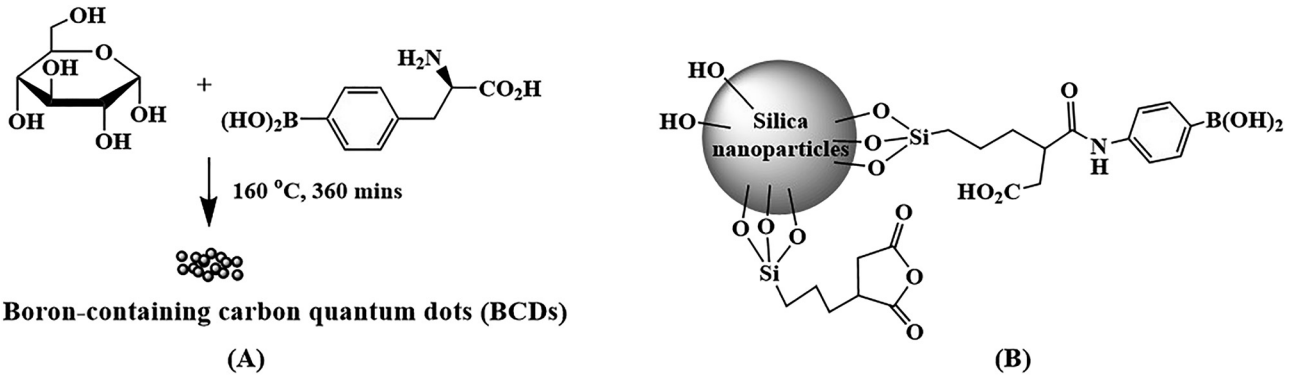

Figure 9: A schematic diagram of the synthesis of the boron-containing carbon quantum dots (BCDs) nanoparticles (A), and the boron isotope-bonded silica nanoparticles (B).

continuous improvement of the technology for preparing quantum dots, quantum dots have an increasing tendency to be used in biological research.

A kind of boron containing CQDs has been reported in patent CN111204736B [92]. The nanomaterial has potential applications in tumor diagnosis and BNCT treatment. In the art, glucose and BPA are used as raw materials to synthesize boron containing carbon quantum dots (BCDs), which have fluorescence luminescence properties similar to those of carbon quantum dots *in vitro* and *in vivo*. Experiments in the present invention have shown that the BCDs synthesized using glucose and BPA as raw materials (Figure 9A) that can target brain tumors and other tumor tissues, and accumulate at tumor sites, while BCDs in healthy tissues can be rapidly metabolized and excreted. This characteristic property provides conditions for achieving excellent therapeutic effects in BNCT. The boron containing carbon quantum dots of the present invention have good biocompatibility and excellent *in vivo* fluorescence imaging effects.

Boron nanotubes and boron quantum dots

Boron nanotubes (NBTs) are probably the most efficient nanomaterials used as a BNCT agent due to their high boron content. The BNTs can lead to the creation of a series of boron nanostructures, such as boron nanoribbons and nanowires. The quantum dots of boron are another new quantum material after the CQDs. Boron quantum dots (BQDs) do not only have the characteristics of low toxicity, chemical inertness, no light flicker and easy functionalization like boron nitride quantum dots and BC_x quantum dots, they also have a strong affinity with cell tissues so that they can be used to prepare boron-containing drugs for boron neutron capture therapy. However, due to the complexity of boron structure, the preparation method of BQDs has the disadvantages of high cost, long process cycle and high toxicity of raw materials, which significantly limits the application of boron quantum dots in biological sciences. At present, the methods used to prepare boron nanostructures mainly focus on magnetron sputtering, chemical vapor deposition, and ultra-high vacuum molecular beam epitaxy.

Boron, as the fifth element, has a carbon-like sp^2 hybrid orbital, with short covalent bond radii and diverse valence states, which are conducive to the formation of low-dimensional boron allotropes, such as: boron alkene, boron nanotubes, cage structures, etc. However, the strati form boron phase material corresponding to boron alkene has not been found in nature, and the preparation method of CQDs cannot be directly applied to BQDs.

The patent CN110194464A [93] proposes a method of preparation for high-yield BQDs using the high-energy ultrasonic technology with auxiliary chemical stripping at room temperature and atmospheric pressure, which can solve the shortcomings of high cost, long process cycle and high toxicity of raw materials in the existing BQD preparation methods. The steps are as follows: disperse the boron powder in an organic solvent and stir evenly to obtain a mixed solution containing boron particles, add hydrogen peroxide steam generator and boric acid powder, crush it with high-energy ultrasonic to obtain a primary product solution, then add sodium borohydride, centrifuge, and obtain b BQDs. This patented invention uses boron powder as a boron source for the preparation of fluorescent BQDs, organic solvent isopropanol and tetrahydrofuran as dual-drive chemical etchants, and uses high-energy ultrasonic with crushing auxiliary liquid phase stripping method to obtain BQDs. The resulting BQDs are uniform in size, with light green fluorescence, which can be used as boron-containing drugs for boron neutron capture therapy and have the potential for large-scale production and broad commercial application prospects.

Wang et al. introduced a method for preparing boron oxide quantum dots in patent CN112250081B [94]. First, ammonium pentaborate and boric acid are dissolved in deionized water and stirred evenly to obtain a uniformly mixed solution of ammonium pentaborate and boric acid. Then, a hydrothermal reaction is conducted to obtain a primary product solution. Then, a reducing agent solution is added, and the mixture is fully stirred before freeze drying to obtain the boron oxide quantum dot powder, finally. The structure of the material is controllable through the optimization of the precursor. The isolated boron oxide quantum dots have uniform size and blue fluorescence, which can be used as boron containing drugs for boron neutron capture therapy.

In relative work, patent CN115607668A [95] depicts the preparation of boron-rich nanoparticles for application to boron neutron capture therapy. First, ultra-small boron rich quantum dots with particle size ≤10 nm were synthesized through different preparation methods. Then, transition metal ions, such as Fe^{3+} and Cu^{2+}, coordinated with the boron hydroxyl group of boron rich quantum dots to assemble them into boron rich nanoparticles with large particle size. This boron rich nanomaterial preparation improves the tumor retention effect and increases the boron content at the tumor site, which can meet the boron dose requirements of BNCT. Secondly, through the low pH with high expression of H_2O_2 and GSH intelligent response of TME, the above large particle sized boron rich nanoparticles with high tumor retention are reassembled into ultra-small sized particles of boron rich quantum dots with strong penetration ability. They have the ability to target tumor nuclei, which can significantly improve the therapeutic effect of BNCT on malignant tumors. In addition, the metal ions in boron rich nanoparticles are reduced to their lower oxidation states (such as Fe^{2+}, Cu^{+}, etc.) by the highly expressed GSH in TME, and then Fenton or Fenton-like reactions occur with H_2O_2 in TME to generate strong oxidizing hydroxyl radicals, achieving chemo-dynamic therapy (CDT). In summary, this invention constructs a boron-rich nanoparticle with variable particle size based on TME intelligent response through a simple process. As a boron containing drug application for BNCT, it can achieve the collaborative treatment of BNCT and CDT based on the nucleus, and effectively solves the contradiction between large particle size but poor permeability of boron containing nanoparticle drugs, and small particle size and poor tumor retention.

Boron nitride nanotubes and quantum dots

The boron nitride nanotubes (BNNTs) are a structural analog of CNTs. Compared to CNTs, BNNTs have excellent chemical and thermal stability. The disadvantage is that the method of preparation is complicated, the cost is high, the toxicity problem has not been completely solved, and the targeting ability needs to be improved. The patent CN113753866A [96] discloses a hexagonal boron nitride nanocrystalline material and its synthesis in solid-state along with other properties. First, the precursor of boric acid/melamine was prepared from solution by co-precipitation, and then ultrafine hexagonal boron nitride nanocrystals of a particle size ≤20 nm, with narrow particle size distribution and in high purity, were prepared by high-temperature heat treatment, followed by centrifugal washing and dialysis in air. The main focus is to use boric acid/melamine co-precipitate as the precursor, and during the heat treatment process at a specific temperature, the reaction between boric acid and melamine occurs to generate hexagonal boron nitride (h-BN) phase. Upon exposure to the air, the generated h-BN phase reacts with oxygen in the air to form boron oxide and ammonia, which together form a special h-BN nanomaterial. Later, by laying a reaction bed with a thickness of no more than 2 cm, using air to *in-situ* etching, the poorly crystallized portion of the continuously generated h-BN phase produces ultrafine h-BN nanoparticles with relatively uniform particle size and high crystallinity. The h-BN nanoparticles have a particle diameter of ≤20 nm, a particle diameter of ≤10 nm under optimized conditions, and a narrow particle size distribution. The resulting h-BN nanoparticles have good hydrophilicity and can be used in various scientific fields, including biomedicine.

The patent CN115040646A [97] provides a method for preparing tumor antigens based on BNCT and its application. The method of the present invention is based on chemical vapor deposition (CVD) and ultrasonic treatment in water to construct boron nitride nanoparticles, and then polyvinyl pyrrolidone (PVP) is used to modify the boron nitride nanoparticles to obtain BN@PVP. Finally, the Toll-like receptor agonist R837 was loaded into BN@PVP to obtain BN-R837@PVP which was subsequently used in the BNCT treatment. When the method of the present invention is applied to BNCT treatment, it improved the cross-presentation efficiency of dendritic cells, effectively activated the anti-tumor immunity of cells, and caused the expansion of CD4+ cells and CD8+ T cells in tumors. This also increased the infiltration of CD4+ and CD8+ T cells in tumor tissue, effectively inhibited the growth and metastasis of distal tumors, and also stimulated individuals to exhibit strong memory T cell effects, which can induce efficient and long-term anti-tumor immunity *in vivo*. It provided a new idea for developing a new type of BNCT tumor vaccine.

Li et al. represented a method for preparing boron nitride nanomaterials on the pore surface of porous

ceramics in patent CN115160023A [98]. The method comprises the following steps: (1) mixing boron source raw material powder with metal powder by ball milling to obtain boron source precursor powder; (2) preparing a metal coating on the porous alumina ceramic pore surface; and (3) producing boron nitride nanomaterials by high-temperature annealing on the pore surface of porous ceramics with metal coating. The growth of boron nitride nanomaterials on the porous ceramic pore surface in the present invention significantly increases the specific surface area of the porous ceramic matrix and has excellent super hydrophobic properties.

Boron nitride quantum dots (BNQDs) are a new type of two-dimensional material with high specific surface area, high drug loading capacity, good biocompatibility and optical stability. In the treatment of tumors, it can be used as drug carriers or photodynamic/photothermal/radiotherapy probes; at the same time, it can also realize multimodal combined diagnosis and treatment. However, there continue to be challenges for BNQDs, such as addressing their toxicity and improving their targeting capacity. In the region, Xing et al. describe the preparation of a quantum dot of graphene doped with boron nitrogen and its application as medicines for boron neutron capture therapy [99]. The boron nitrogen doped graphene quantum dots are synthesized using graphene quantum dots and aqueous solution of ^{10}B-enriched boric acid as raw materials. The boron nitrogen doped graphene quantum dots have high boron content, excellent optical properties, good biocompatibility, and low toxicity to achieve *in vivo* fluorescence imaging. Experiments have proved that the quantum dots can also target breast cancer tumors and enrich in breast cancer tumor sites, but boron nitrogen doped graphene quantum dots can be rapidly metabolized and discharged from healthy tissues. These properties make boron nitrogen doped graphene quantum dots suitable as a new boron delivery agent to achieve the diagnosis and BNCT treatment of breast cancer tumors.

Mesoporous silica nanoparticles

Nano-scale mesoporous silica is a non-toxic, tasteless, pollution-free and degradable non-metallic material, and it is one of the most widely studied nanomaterials in the field of biomedicine due to its low density, high specific surface area, good biocompatibility and easy modification of surface groups [100]. Generally, these silica particles are between 40 and 400 nm in diameter. Surface charge property can be altered to prevent particles from aggregating in biological media and to achieve prolonged circulation. Furthermore, various nanomachines can be engineered on the surface of the particles to confer the ability to release anticancer drugs upon stimuli, including light and magnetic field exposure.

The patent WO2019181018A1 [101] discloses the easy production of an oligosaccharide and oligopeptide exhibiting excellent specific binding properties to tumor cells which is chemically bonded to ^{10}B isotope of boronated nano-silica particles. The basic skeleton of this nanoparticle is the boron isotope-bonded nano-silica particle as shown in Figure 9B. It provides a drug transport (delivery) material with excellent specific accumulation property to tumor cells for BNCT. The preparation method involves boron isotopes that are chemically bonded to nano-silica particles first, and then oligosaccharides and oligopeptides are further bonded in consideration of the selectivity and accumulation of various types of tumor cells. The porous spherical silica particle diameter used in the present invention is 5–2000 nm, the surface area of which is 100–300 m^2/g, resulting in spherical nano-silica particles, and this large surface area is chemically modified with a reactive functional group.

Tamanoi reported a biodegradable periodic mesoporous organosilica nanomaterial (BPMO) and methods for producing BPMO charged with neutron capture agents in patent US11191836B2 [102]. Thus, the BPMOs loaded with neutron capture agents provide a method of treating cancer, immunological disorders and other disease by utilizing a neutron capture therapy modality, including but not limited to rheumatoid arthritis, ankylosing spondylitis, and other cellular diseases, and Alzheimer's disease. In certain embodiments, the nanomaterials comprise mesoporous silica nanoparticles ("MSN" or "MSNs", as appropriate). In a further embodiment, an MSN of the invention comprises a bio-degradable bond within the framework of the MSN. In general, biodegradable MSNs tuned for biodegradation by incorporating disulfide, tetrasulfide bonds, or protease sensitive bonds are referred as BPMO.

In addition, the patent CN110302381B [103] provides a mesoporous silica nanospheres with carborane modified on the surface and its preparation method, wherein carborane is connected to the surfaces of the mesoporous silica nanospheres in a covalent bond mode for the first time. The modified material has no toxic effect on organisms, can be applied to a drug delivery system, and also has the potential of being used as a boron carrier for boron neutron capture treatment. The preparation steps are: (a) under the protection of nitrogen, dissolving carborane in anhydrous ether, dropwise adding *n*-butyl lithium, stirring for several hours at room temperature, adding bromopropyltrimethoxysilane, stirring the mixture for 20 h at room temperature, adding water for quenching, extracting mother liquor with ether, and performing vacuum concentration to obtain mono-substituted

trimethoxysilylpropylcarborane; (b) mesoporous silica nanospheres were synthesized by TEOS, CTAC, cyclohexane, alkali and water, and then the surfactant template was extracted with acid ethanol solution; (c) a certain amount of silicon dioxide nanospheres with the template removed were ultrasonically dispersed in toluene, adding mono-substituted trimethoxy propyl carborane, stirring at 90–100 °C for 12–24 h, centrifuging, washing with absolute ethyl alcohol for 3–4 times, and vacuum drying for 6 h.

In CN114984247A [104], Zhang et al. illustrate a method of preparing liver cancer targeting the hollow mesoporous silica of loaded carbosilane (LBHMSi). The hepatoma targeted carbosilane loaded hollow mesoporous silica was prepared using hollow mesoporous silica modified with lactonic acid/lipoctanoic chitosan as a drug carrier and orthocarbosilane as a boron-containing drug group. The bioassay results showed that the targeted material has a strong selective enrichment ability on liver cancer cells, while exhibiting good biocompatibility and low toxicity. It has strong cell cycle arrest, apoptosis induction, and killing effects on liver cancer cells and can synergistically play antioxidant and anti-inflammatory roles in boron neutron capture therapy. Thus, the reduction of the side effects of radiotherapy has a good prospect for BNCT treatment.

Noble metal nanoparticles

Nanomaterials involving noble metals include mainly silver, gold, ruthenium, rhodium, palladium and platinum. Silver nanomaterials have the largest production and are widely used in wound dressing and washing machine disinfectants, depending on its antibacterial activity. Gold nanomaterials, due to their good biocompatibility and chemical stability, are a hot topic in terms of biomedical and biochemistry detection field in recent years. The patent CN107983341B [105] discloses a noble metal nanoparticle adsorbed with boron cluster compound and its preparation method and application. In the production of these nanoparticles, the boron cluster compound acts as a reducing agent in solutions containing the noble metal ions, including Ru, Rh, Pd, Ag, Pt, Au, etc. In addition, the negatively charged property of the boron cluster compound itself allows it to attach to the surface of the noble metal nanoparticles, limiting the further growth of the metal particles. Thus, the noble metal nanoparticles are adsorbed with borane clusters compounds with good dispersion in solution. The invented method is relatively easy to control reaction conditions such as feed ratio, temperature, time and precious metal ion concentration, etc. The preparation process is very simple, under mild conditions, high reaction efficiency, only simple mixing is required, and after a period of time, noble metal nanoparticles that are adsorbed with boron cluster compounds of uniform particle size can be produced, while the whole preparation process does not pollute the environment.

Ferritin nanoparticles

Ferritin nanoparticle (FNP) is an attractive protein nanoplatform for *in vivo* antigen delivery, presentation and immune stimulation. It has well-defined spherical architecture with outer diameter of 12 nm, a size suitable for rapid penetration of tissue barrier and draining to lymph nodes. The FNP can be efficiently phagocytosed by dendritic cells for antigen presentation *in vitro*. In addition, FNP demonstrates remarkable thermal and chemical stability, and it is particularly amenable to reconstitution through controlled disassembly/reassembly process.

The patent CN114259563A [106] discloses a boron delivery agent using ferritin nanoparticles as a carrier and a preparation method thereof. The boron delivery agent provided by the present invention uses ferritin nanoparticles as the carrier for the delivery of boron compounds, and its receptor TfR1 is a tumor marker molecule. Therefore, ferritin has the characteristics of directly targeting tumor cells and tumor tissues that overexpress the TfR1 receptor, and can be enriched in tumor tissue, with a small distribution in other tissues and organs. There are also many modification sites on the surface of ferritin nanoparticles. Through modification of tumor targeting molecules, it can improve their tumor targeting and achieve high concentration enrichment of boron compounds in tumor tissue. The ferritin nanocarrier provided by the present invention has stable physical and chemical properties, is not easily denatured, has strong resistance to external environments, has a wide range of applications, and has a long shelf life of the prepared product. It can withstand high concentrations of denaturants and high temperatures of 70–80 °C without denaturing. The boron delivery agent provided by the present invention has a simple loading method for boron compounds. Using the pH change complexation method, boron reagents can be loaded, and the pH of the ferritin solution can be adjusted to 2.0. The protein shell structure will disintegrate. When the pH recovers to above 7.0, the disintegrated protein subunits can be reassembled into complete ferritin, thereby encapsulating the blended boron compounds in the core of ferritin nanoparticles. The boron delivery agent not only has tumor targeting properties, but

also has advantages such as stable physical and chemical properties, simple loading methods for boron compounds, good biocompatibility, good dispersibility, and uniform particle size.

Conclusions

The BNCT is a promising binary radiation therapy. It selectively destroys cancer cells while preserving normal tissue cell. There are two key factors for the successful implementation of BNCT. One of that is a sufficient number of thermal neutrons need to be irradiated into the tumor area, and at least a neutron flux of $10^9/cm^2s$. The second is to have a sufficient number of ^{10}B atoms, preferably 10^9 or more ^{10}B atoms, accumulated in tumor cells and able to stay for a long time in each tumor cell. In recent years, the accelerator-based neutron source equipment has made some progress, and the equipment technology will be more mature in the future.

In the field of boron delivery agents, only two boron agents, BSH and BPA are still applicable in clinical practice. Though they all have their respective benefits and have been used in BNCT clinical trials for many years. There are also inherent limitations of the two drugs such as relatively low bio-selectivity and low water solubility. Therefore, it is still hoped that better and more effective new boron delivery agents will be developed to promote further development of BNCT in clinical practice. It is well recognized that an effective boron delivery agent must have good tumor specificity and, simultaneously, be able to deliver a sufficient amount of ^{10}B into tumor cells (preferably near the nucleus) and have a long retention time, while metabolizing rapidly in normal tissues and blood to achieve a high tumor to normal tissues (T/N) and tumor to blood (T/B) boron concentration ratio. Because of the strict criteria, the development of new boron delivery agents will be a key challenge in meeting all requirements.

In order to properly tackle the boron agent problem, various boron distribution systems are being studied in different laboratories. Small molecule-based boron agents typically have a strong druggability and production achievable under the Good Manufacturing Practices (GMP), but the quantities of boron delivered are limited. Nanomaterial and nanoparticle distribution systems demonstrate a high ability to deliver and release drugs in a controllable way on a target lesion. Several nano-based medicines have been approved by the FDA for clinical application. However, there are drawbacks to these nanocarriers as well. For example, liposomes are low stable and tend to agglomerate; antibody-drug conjugates (ADCs) have a narrow therapeutic window and thus lead to dose-limiting toxicity; metal nanoparticles, carbon nanotubes, boron-nitrogen nanotubes are not biodegradable and poorly water-soluble. For boron-containing nanocarriers, significant amounts of boron atoms could be transported to tumor tissues, but further studies are needed for their bioselectivity, bioavailability, systemic toxicity and GMP production. The development of new boron agents will rely on a multidisciplinary approach and cooperation from researchers across many fields, including medicinal chemistry, radiation oncology, nuclear physics and radiobiology. It is believed that in the future, BNCT will continue to receive attention. With further breakthroughs in various technologies, BNCT can become a competitive mainstream cancer treatment plan.

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